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credit life insurance policies for these years were in the mean amount of $1,292,566.

Defendant contends that the dollar amount ($1,292,566) of the gross unearned premium reserve that plaintiff reported is not a close approximation of the tabular reserve that would have been required in 1964. Defendant also asserts that plaintiff may not use the Illinois standard that permits credit life reserves be based on 130 percent of the appropriate mortality table. Defendant asserts that the gross unearned premium reserves plaintiff reported were approximately 184 percent of the amount the tabular reserve would have been if computed at 100 percent rather than at 130 percent of the appropriate mortality table.

The Illinois Insurance Department's directive that authorized use of the 130 percent factor was to all insurance companies writing credit life insurance in Illinois and was not limited in scope to business written in Illinois. Plaintiff is permitted to use the highest aggregate reserve requirement of any state in which it transacts business for the purpose of computing its reserves. This principle is incorporated in Treasury regulations insofar as it affects computation of total reserves.[38] Accordingly, in 1964, plaintiff was required, with respect to its Illinois business, to compute its credit life reserves on the basis of 130 percent of the appropriate mortality table. Plaintiff's use of the 130 percent factor in its computation of hypothetical tabular reserves as a basis for comparison with its gross unpaid premium reserve was appropriate.

The dollar amounts that plaintiff reported as its credit life reserves were reasonably approximate to the amounts that would have been derived from computations from the appropriate mortality tables. The amounts reported satisfy the requirement that the reserve be estimated on a tabular basis. In any event, the dollar amount of reserves established by plaintiff on its credit life policies included the lesser amount which would have been derived from a computation based upon 130 percent of the appropriate table, which, when included in the numerator of the qualification fraction, would also confirm plaintiff's status as a life insurance company in 1964.

On the basis of the foregoing, plaintiff's reserves on its credit life policies satisfy the requirements of the statutory definition in section 801(b). Other reserve items are in dispute, and the parties have briefed their respective positions thereon. As to these other items, decision has been requested to resolve status questions for years not now pending before the court. Inasmuch as disposition of the credit life reserve question resolves plaintiff's status as a life insurance company for purposes of this case, no decision is made on the other items in dispute.

38. Treas.Reg. § 1.801–5(a)(3) states, in part:

"The term 'total reserves' does not, however, include deficiency reserves (within the meaning of section 801(b)(4) and paragraph (e)(4) of § 1.801–4), even though such deficiency reserves are required by State law. In determining total reserves, a company is permitted to make use of the highest aggregate reserve required by any State or Territory or the District of Columbia in which it transacts business, but the reserve must have been actually held during the taxable year for which the reserve is claimed. * * *"

See also Continental Ins. Co. v. United States, 474 F.2d 661, 668, 200 Ct.Cl. 552, 564–65 (1973), where the court states:

"* * * Courts have explicitly recognized that, for federal tax purposes, state rules on reserves apply across the board to all of a company's business, in the same way that such rules are applied by the states themselves. * * *"

Application of Everette L. MAY and Nathan B. Eddy.

Appeal No. 77–600.

United States Court of Customs and Patent Appeals.

April 20, 1978.

Appeal was taken from a decision of the Patent and Trademark Office Board of

Appeals, Serial No. 45,553, sustaining an examiner's rejection of claims 1–13 for alpha-levo benzomorphan analgesics having nonaddictive and morphine antagonistic properties. The Court of Customs and Patent Appeals, Lane, J., held that: (1) certain prior art was a technical anticipation of claims 1 and 6; (2) the record established that the claimed compounds did, in fact, produce nonaddictive analgesia, which would have been totally unexpected to those skilled in the art; (3) findings of fact entered of record in prior interference proceedings, relating to the desirability of nonaddictive analgesics of the morphine class, were both relevant and admissible, and (4) evidence indicated that the subject matter of appealed claims 2–5 and 7–13 would not have been obvious to one of ordinary skill in the art.

Affirmed in part; reversed in part.

1. Patents ⇐18, 66(1.12)

Prior art disclosing compound which was species within genus of compound described in claims of application was technical anticipation of such claims and warranted rejection on grounds of obviousness, since lack of novelty is epitome of obviousness. 35 U.S.C.A. § 103.

2. Patents ⇐27(1)

Discovery of hitherto unknown property of species of compound disclosed by prior art does not constitute "new use." 35 U.S.C.A. § 100(b).

See publication Words and Phrases for other judicial constructions and definitions.

3. Patents ⇐65

Prior art reference does not fail as anticipation merely because it does not contain description of subject matter of appealed claim in ipsissimis verbis. 35 U.S.C.A. § 103.

4. Patents ⇐45

Novelty of optical isomer of compound is not negated by prior art disclose of its racemate.

5. Patents ⇐113(6)

Record, on application for alpha-levo benzomorphan analgesics having nonaddictive and morphine antagonistic properties established that compounds described in claims did, in fact, produce nonaddictive analgesia.

6. Patents ⇐36(3)

Evidence, in proceedings on application for alpha-levo benzomorphans analgesics having nonaddictive and morphine antagonistic properties established that nonaddictiveness of analgesic compounds disclosed would have been totally unexpected to those skilled in the art. 35 U.S.C.A. § 103.

7. Patents ⇐36(3)

Where record on application for chemical compound reflects both expected beneficial result and unexpected beneficial result, it is necessary to determine weight to be accorded each prior to making ultimate determination on issue of obviousness. 35 U.S.C.A. § 103.

8. Patents ⇐113(6)

Findings of fact entered of record in prior infringement suit, reflecting desirability of nonaddictiveness in analgesic compounds of morphine class, were relevant and admissible evidence in proceedings on application for alpha-levo benzomorphans analgesics having nonaddictive and morphine antagonistic properties where compounds disclosed in application exhibited both expected beneficial result of analgesia as well as unexpected beneficial result of nonaddictiveness. 35 U.S.C.A. § 103.

9. Patents ⇐36(3)

Evidence, in proceedings on application for alpha-levo benzomorphan analgesics having nonaddictive and morphine antagonistic properties, established that subject matter of claims 2–5 and 7–13 in application would not have been obvious to one of ordinary skill in art. 35 U.S.C.A. § 103.

Jerome M. Teplitz, Washington, D. C., attorney of record, for appellants; Marvin R. Stern, John C. Holman, Washington, D. C., Thomas G. Ferris, Norman J. Latker, Bethesda, Md., of counsel.

Joseph F. Nakamura, Washington, D. C., for the Commissioner of Patents; Gerald H. Bjorge, Washington, D. C., of counsel.

Before MARKEY, Chief Judge, and RICH, BALDWIN, LANE and MILLER, Judges.

LANE, Judge.

This is an appeal from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) sustaining the examiner's rejection under 35 U.S.C. § 103 of claims 1–13 of application serial No. 45,553,[1] filed June 11, 1970, for "Alpha-Levo Benzomorphan Analgesics Having Non-Addictive and Morphine Antagonistic Properties." We affirm the rejection of claims 1 and 6, and reverse the rejection of claims 2–5 and 7–13.

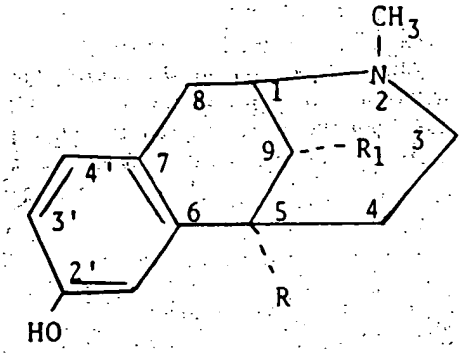
BACKGROUND

The Invention

Broadly stated, the subject matter of this appeal involves a certain class of analgesic compounds, *i. e.*, pain-relieving drugs, and the method of using them to effect analgesia. More specifically, appellants characterize their invention as residing in the discovery that the acid addition salts of certain levo and alpha-levo isomers of N-methyl benzomorphan exhibit a unique combination of neuropharmacological properties, to wit, analgesic potency comparable to that of morphine coupled with *nonaddictiveness* and the absence of other undesirable side effects.

The appealed claims read:

1. A method of affecting [sic] analgesic and morphine antagonistic activity without producing physical dependence in animals which comprises administering to an animal an effective dosage of an acid addition salt of the levo isomer of a compound of the structure



where R is a lower alkyl group and R_1 is hydrogen or a lower alkyl group.

2. The method of claim 1 wherein said compound is α-(-)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

3. The method of claim 1 wherein said compound is (-)-5-methyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

4. The method of claim 1 wherein said compound is (-)-5-ethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

5. The method of claim 1 wherein said compound is α-(-)-5-propyl-9-methyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

6. The method of claim 1 wherein said salt is the hydrochloride.

7. The method of claim 6 wherein said compound is α-(-)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

8. The method of claim 6 wherein said compound is (-)-5-methyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

9. The method of claim 6 wherein said compound is (-)-5-ethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

10. The method of claim 6 wherein said compound is α-(-)-5-propyl-9-methyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

11. A pharmaceutical composition for internal administration having an analgesic, non-addictive, morphine-antagonistic effect which comprises a pharmaceutical carrier and an effective amount of an acid addition salt of α-(-)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.

12. The composition of claim 11 wherein said salt is the hydrochloride.

1. This application is a continuation-in-part of application serial No. 801,209, filed February 20, 1969, which is in turn a continuation-in-part of application serial No. 643,382, filed June 5, 1967; both applications are now abandoned.

13. The composition of claim 11 wherein said salt is the acetate.

An understanding of the subject matter involved in this appeal, as should be apparent from the claims reproduced above, requires, at the very least, a familiarity with certain aspects of stereochemistry and pharmacology.

Appellants' compounds exhibit the condition known as stereoisomerism, namely, for a given R and R_1, isomers will exist that differ from each other only in the way the atoms are oriented in space (but are like one another with respect to which atoms are joined to which other atoms). Two stereoisomers will be either enantiomers or diastereoisomers, depending on whether or not the two isomers are mirror images of each other. In appellants' compounds, when R_1 is substituted, *i. e.*, when hydrogen is replaced, the resulting structure exists as two pairs of diastereoisomers, referred to by either the prefix alpha (α) or beta (β), each pair differing from each other in the spacial orientation of the C–9 substituent. Each diastereoisomeric form, itself, has two separate enantiomers, referred to by either the prefix levo (-) or dextro (+), whose structures differ only in being mirror images of each other. Enantiomers are sometimes referred to as optical isomers since the levo and dextro forms are capable of rotating the plane of polarized light to the left and right, respectively. A mixture of equal parts of the levo and dextro forms of a compound is known as a racemate and is referred to by the prefix (±). A racemic mixture is optically inactive.

Applying the above nomenclature to the appealed claims, when R_1 is substituted, the claims are limited to the levo enantiomer of the alpha diastereoisomer (the broken line from C–9 to R_1 signifies the alpha isomer; a solid line from C–9 to R_1 would signify the beta isomer). When R_1 is not substituted, the claims are limited to the levo enantiomer (there is no diastereoisomerism unless R_1 is substituted).

Switching to pharmacology, in order to determine the neuropharmacological properties of a compound, certain laboratory test properties are ascertained. Those relevant here will briefly be discussed.

Analgesic Activity (E.D.50) is the dose in mg/kg which produces the desired effect in 50% of a given mouse population. A low value is indicative of a potent analgesic.

Physical Dependence Capacity (PDC) is a measure of whether the test drug will suppress withdrawal symptoms in morphine-addicted monkeys which have had their regular morphine injections withheld. PDC is rated as high, intermediate, low, or no capacity. PDC is used as a measure of addiction potential.

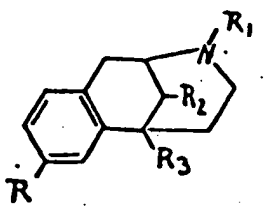
Morphine Antagonism is a measure of whether the test drug is capable of producing withdrawal symptoms in a non-withdrawn, morphine-addicted monkey. The antagonist activity is measured against nalorphine, which is the standard morphine antagonist. The precipitation of withdrawal symptoms in addicted monkeys has been taken as evidence that a drug may be assumed to be nonaddicting in man.

Toxicity (L.D.50) is the dose of the test drug in mg/kg which is lethal to 50% of a mouse population. A high value is indicative of low toxicity.

Therapeutic Index (L.D.50/E.D.50) is a mathematical expression of the safety margin of a compound. A high value is indicative of an effective analgesic which is relatively nontoxic.

Prior Art

May,[2] which we view as the most pertinent reference, discloses a broad genus of benzomorphans represented by the formula



2. U.S. Patent No. 3,138,603, issued June 23, 1964, for "New Benzomorphans (Methanobenzazocines) and Preparation Thereof."

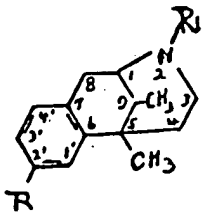
wherein R is a member selected from the group consisting of hydrogen and the hydroxy, alkoxy and acyloxy radicals; R_1 is a member selected from the group consisting of hydrogen, methyl, straight chain alkyl, and aralkyl radicals; R_2 is a member selected from the group consisting of hydrogen alkyl, methylene and substituted methylene radicals; and R_3 is a member selected from the group consisting of hydrogen and the alkyl radicals—and especially compounds of such formula wherein the alkyl portions of the said members contain from 1 to 4 carbon atoms, with the limitation that when R_2 is hydrogen R is other than hydrogen.

As to the above compounds May states:

Certain products of this invention have been discovered to show superior analgesic and tranquilizing powers of a potentially medically useful type and there is evidence that they may have less addiction potential and toxicity than presently-used pain-relieving drugs, as well as other advantages including possible oral effectiveness.

It is disclosed that these compounds can be provided as racemates, as separated optical isomers, and as separated diastereoisomers. It is further disclosed that virtually all of the neuropharmacologic activity is due to the levo, as opposed to the dextro, isomer.

May states that of the benzomorphans forming the subject of his invention, those which have been evaluated by animal tests include:



wherein R is a member selected from the group consisting of hydrogen, hydroxy and methoxy and R_1 is a member selected from the group consisting of methyl and phenethyl, R_1 being methyl when R is other than hydroxyl.

The benzomorphans corresponding to the above general formula were preferably administered in the form of their salts, "the hydrobromide and hydrochloride salts being especially suitable."

Of particular significance is the express disclosure of α-(-)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, which is a species within appellants' claim 1; May is silent on whether or not this specific compound was found to be addictive, but he does state that its therapeutic index is superior to that of morphine sulfate. With respect to α-(±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, the racemate of the above alpha-levo compound, May indicates that it showed physical dependence liability in monkeys comparable to morphine, and that the beta racemate is the analgesically more potent diastereoisomer. Finally, with respect to the α-(-) and β-(±) forms of 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, May comments that they are "promising candidates for clinical use."

Chignell et al.[3] expressly disclose, *inter alia*, α-(±)-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan, which is the racemate of the compound in appealed claims 5 and 10; the beta diastereoisomer is also disclosed, and is indicated to be analgesically more potent than the alpha isomer. They further indicate that the alpha racemate has an E.D.50 comparable to morphine, while having, like other members of the alpha series, little or no capacity to suppress withdrawal symptoms in monkeys, *i. e.*, little or no PDC. It is stated that a nearly complete separation of these two parameters is seen with the alpha isomer.

Beckett et al.[4] indicate that the analgesic activity of the benzomorphans resides chiefly in the levo isomers.

3. Chignell, Ager, & May, *Structures Related to Morphine. XXVIII. Alternative Syntheses of α- and β-2,9-Dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan*, 8 J. MEDICINAL CHEMISTRY 235 (1965).

4. Beckett & Anderson, *The Determination of the Relative Configuration of Morphine, Levorphanol and Laevo-Phenazocine by Stereoselective Adsorbents*, 12 J. PHARMACY AND PHARMACOLOGY 228T (1960).

Fullerton et al.[5] expressly disclose, *inter alia*, the following isomers: α-(+)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (the dextro isomer of the compound in appealed claims 2, 7, and 11–13); (±)-5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan (the racemate of the compound in appealed claims 3 and 8); (±)-5-ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (the racemate of the compound in appealed claims 4 and 9).

They further disclose that the beta compounds are analgesically more potent than the alpha counterparts, and that the activity resides in the levo enantiomers.

Archer et al.[6] provide a general discussion of the analgesic-antagonist activity of various N-substituted benzomorphan compounds. Specifically, they are concerned with substituents at the "N" position *other* than CH_3 (the appealed claims require CH_3 to be the N-substituent). Since we view this reference as the least pertinent, no further discussion of it is deemed necessary.

Rebuttal Evidence

The evidence submitted by appellants includes, *inter alia*, two affidavits by Everette May and one affidavit by Nathan Eddy (these three affidavits will hereinafter be referred to as the May-Eddy affidavits). Collectively, these affidavits provide comparative test data for the following compounds and racemates:

2,5,9-trimethyl-2'-hydroxy-6,7-benzomorphan

α-(-) [May isomer; species within genus claims 1, 6.]

α-(+)

α-(±)

β-(-)

β-(+)

β-(±)

5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan

α-(-) [Compound of claims 2, 7, 11-13.]

α-(+) [Fullerton et al. isomer.]

α-(±)

β-(-)

β-(+)

β-(±)

5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan

(-) [Compound of claims 3, 8.]

(+)

(±) [Fullerton et al. racemate.]

5. Fullerton, May, & Becker, *Structures Related to Morphine. XXIII. Stereochemistry of 5,9-Dialkyl-6,7-benzomorphans*, 27 J. ORGANIC CHEMISTRY 2144 (1962).

6. Archer, Albertson, Harris, Pierson, & Bird, *Pentazocine. Strong Analgesics and Analgesic Antagonists in the Benzomorphan Series*, 7 J. MEDICINAL CHEMISTRY 123 (1964).

5-ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan

(-) [Compound of claims 4, 9.]

(+)

(±) [Fullerton et al. racemate.]

5-propyl-9-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan

α-(-) [Compound of claims 5, 10.]

α-(+)

α-(±) [Chignell et al. racemate.]

The above were tested for E.D.50, PDC, morphine antagonism, and L.D.50. Of all the substances tested, *only the levo [(-)]*[7] *and alpha levo [α-(-)] isomers* exhibited the *combined* test properties of an E.D. 50 comparable to that of morphine sulfate, morphine antagonistic activity, no PDC, low toxicity, and a relatively high therapeutic index. Moreover, only the levo[8] and alpha-levo isomers exhibited morphine antagonism.

A fourth affidavit, by Arthur Jacobson, an expert in the field of pharmacology whose credentials have not been challenged, was also submitted. Since this affidavit plays a significant role in the disposition of this appeal, the portions which we view as most pertinent are reproduced below:

6. That agonist-antagonists which are defined as those analgesics which display antagonism to some of the pharmacological effects of narcotic analgesics, such as morphine and heroin, exhibit at least three biological properties which are not exhibited by narcotic analgesics, to wit:

(1) They do not have addiction-liability of the opiate type.

(2) Tolerance to them is not developed.

(3) They do not produce the depth of respiratory depression . . . which is produced by the opiates.

* * * * * *

10. That medicinal chemists have for many years been searching for an analgesic drug which has the analgesic potency of morphine, but without morphine's side effects and addiction liability. . . .

11. That there are many clinical situations in which respiratory depression produced by narcotic analgesics would be life-threatening and where the development of tolerance to the analgesic impairs its effectiveness. A physician concerned with relieving severe chronic pain due to non life-threatening causes . . . has a very difficult decision to make when prescribing addictive analgesics. The discovery of a non-addictive analgesic with analgesic potency comparable to that of morphine would eliminate a major medical problem and would be of inestimable value.

* * * * * *

13. . . . Since analgesia and addiction liability cannot reliably be predicted on the basis of chemical structure the discovery of May and Eddy that the optical resolution [the separation of the dextro and levo isomers from the alpha racemic mixture] of N-methyl benzomorphans produces agonist-antagonist compounds which exhibit morphine-like analgesia but relatively weak antagonism

7. The levo isomers of the C-9 unsubstituted compounds, *i. e.*, those compounds which do not exhibit diastereoisomerism.

8. See note, 7, *supra*.

was unexpected and unpredictable. Such a combination of properties could not have been predicted because such a combination of properties had not previously been established for any of the N-methyl benzomorphans.

14. That the combination of properties exhibited by the claimed compounds, i. e. analgesic potency comparable to that of morphine plus relatively mild morphine antagonism without Physical Dependence Capacity, . . . based upon the references cited by the examiner, . . . was unpredictable. This combination of properties is of great potential clinical importance since an analgesic with the potency of morphine without its addiction liability will permit the clinician to effectively control pain in cases where morphine or other addictive analgesics cannot or should not be used because of the adverse and dangerous side effects associated with them.

Appellants also submitted an article by *Gates et al.*[9] which discusses the significance of morphine antagonism. *The article indicates that the precipitation of withdrawal symptoms in addicted monkeys has been taken as evidence in the past that a drug may be assumed to be nonaddicting in man.*

Proceedings Below

The board affirmed the rejection of claims 1–13 under 35 U.S.C. § 103 over May and Chignell et al. in view of Beckett et al., Fullerton et al., and Archer et al. It perceived claim 1 as "fully met" by May's disclosure of α-(-)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, a species within the claimed genus. With respect to claims 2–13, after noting that appellants conceded that the claimed compounds, as well as their use as analgesics, would have been prima facie obvious, the board went on to state that since it would have been obvious to use the particular isomers for their analgesic activity, the fact that the prior art did not recognize other properties of these compounds which would make them even more desirable as an analgesic, does not render their use as an analgesic, nor the analgesic composition, non-obvious. This is not a situation, the board noted, where a new use of a structurally obvious compound was found.

OPINION

With respect to both the method and composition claims, appellants have conceded that a prima facie case of obviousness has been established. However, since appellants submitted rebuttal evidence below in response to the prima facie case, the appealed claims must be considered in the light of *all* the evidence, and the resulting decision, that the claimed invention would or would not have been obvious, is to be made in such light. *See In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (Cust. & Pat.App.1976).

Method of Use Claims

[1] We shall first consider claims 1 and 6 since, as will soon become apparent, they stand on a different footing from the other claims. As noted by the board, May expressly discloses the hydrobromide salt of α-(-)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, which appellants admit is a species within the genus of claim 1. Therefore, May is a technical anticipation of claim 1. Appellants' assertions to the contrary notwithstanding, this finding does not constitute a new ground of rejection; lack of novelty is the epitome of obviousness. *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (Cust. & Pat.App.1974).

[2] Appellants contend that May is not an anticipation since claim 1 is limited to a method for effecting nonaddictive analgesia, whereas May only discloses a method for effecting analgesia. Relying on 35 U.S.C. § 100(b), viz., "[t]he term 'process' . . . includes a new use of a known

9. Gates & Montzka, *Some Potent Morphine Antagonists Possessing High Analgesic Activity*, 7 J. MEDICINAL CHEMISTRY 127 (1964).

. . . . composition of matter," appellants conclude that they have discovered a new use for the species disclosed by May. We disagree. Both appellants and May describe methods for effecting analgesia. While appellants have discovered a hitherto unknown property, to wit, nonaddictiveness, of the species disclosed by May, such discovery does not constitute a new use. In *In re Tomlinson*, 363 F.2d 928, 53 CCPA 1421, 150 USPQ 623 (1966), an argument similar to that made by appellants was addressed by the court. There, the claims in question were directed to a process of inhibiting degradation of polypropylene caused by exposure to light by mixing a certain compound (claimed as a genus) with polypropylene. The prior art reference taught mixing a species, which came within the claimed genus, with polypropylene for the purpose of preventing heat degradation during, *inter alia*, extrusion. The court's conclusion in *Tomlinson, supra*, 363 F.2d at 934, 53 CCPA at 1430, 150 USPQ at 628, is equally pertinent here:

> As to the introductory language, 'A process of inhibiting degradation of polypropylene caused by exposure to light,' . . . we do not think these words can serve to patentably distinguish the claimed process from the prior art. That language, in effect, states the *result* of admixing the two materials. While the references do not show a specific recognition of that result, its discovery by appellants is tantamount only to finding a property in the *old composition*, not in the . . . compound for which, it is argued, a new use has been found. [Emphasis in original.]

[3] With respect to claim 6, which recites the use of the hydrochloride salt, appellants assert that May does not "specifically describe" such salt. Nevertheless, May discloses that the benzomorphans corresponding to the generic formula of which α-(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan is a species, are preferably administered in the form of their salts, "the hydrobromide and hydrochloride salts being especially suitable." This statement, coupled with the express disclosure of the hydrobromide salt of α-(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, constitutes an anticipation of claim 6. A reference does not fail as an anticipation merely because it does not contain a description of the subject matter of the appealed claim in *ipsissimis verbis*. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (Cust. & Pat.App.1978). Therefore, since claims 1 and 6 *lack novelty*, we are compelled to affirm the rejection of these claims.

[4] The remaining method of use claims, viz., claims 2–5 and 7–10, critically differ from claims 1 and 6 in that they recite the use of a *novel* compound. As recognized in *In re Williams*, 171 F.2d 319, 36 CCPA 756, 80 USPQ 150 (1948), the novelty of an optical isomer is not negated by the prior art disclosure of its racemate.

Having noted that appellants conceded that it would have been prima facie obvious to use the compounds recited in these claims as analgesics, the board went on to state that "[t]he fact that the prior art does not specifically recognize other properties which when combined with analgesic activity render the obvious method . . . more desirable for the same function does not diminish that teaching [*i. e.*, use as an analgesic] with regard to the method . . for effecting analgesic activity." We cannot accept the board's analysis. In effect, the board cast its conclusion of obviousness in concrete. Its mode of analysis leaves no room for the submission of objective evidence directed to nonobviousness—in this case, appellants' rebuttal evidence that nonaddictive analgesia was unexpected and superior to the known prior art analgesia. *See, e. g., In re Orfeo*, 440 F.2d 439, 58 CCPA 1123, 169 USPQ 487 (1971).

We now proceed to consider the appealed claims in light of *all* the evidence. *In re Rinehart, supra.*

[5] The May-Eddy affidavits establish, by test data, that the compounds named in

the claims have an E.D.50 comparable to that of morphine sulfate, while also exhibiting morphine antagonistic activity with no PDC. We believe the record supports appellants' contention that the compounds recited in the claims exhibit the clinical property of nonaddictiveness. We specifically note paragraphs 6 and 14 of the Jacobson affidavit, reproduced *supra*, and the Gates et al. article, discussed *supra*. Collectively, they support the conclusion that the laboratory test properties of morphine antagonistic activity plus no PDC is evidence of the clinical property of nonaddictiveness, and that morphine antagonistic activity, alone, is also evidence of nonaddictiveness. The PTO has offered no evidence which would suggest that the nexus established by appellants between morphine antagonism (coupled with no PDC) and nonaddictiveness is unsound. We are at a loss to understand the board's cryptic, unsupported statement, "that the morphine-antagonistic properties of the compounds appear to be important only if the animals to which the compounds are administered have morphine in their systems." Whether the board either misunderstood the significance of this laboratory test property or was saying that the evidence of record failed to establish that appellants' compounds were nonaddictive, we do not know. Considering the board's analysis, discussed *supra*, it would appear that proof of nonaddictiveness would not have affected its ultimate conclusion of obviousness. As will be further developed, *infra*, that proof critically affects our conclusion.

Having established that the record supports appellants' contention that their compounds do, in fact, produce nonaddictive analgesia, we must now determine whether or not such a result would have been unexpected to one of ordinary skill in the art.

Appellants have admitted in their brief that one of ordinary skill in the art would have expected that their compounds would be potent analgesics. The solicitor, relying basically on May and Chignell et al., contends that the property of nonaddictiveness would also have been expected. We disagree.

The portion of May on which the solicitor relies states that "there is evidence that . . . [certain products of this invention] may have less addiction potential . . . than presently-used pain-relieving drugs." Preliminarily, it is to be noted that morphine has a high addiction potential; therefore, to say that certain compounds are less addictive than morphine is not to say that they are nonaddictive. More importantly, this passage refers to May's broad genus of benzomorphan compounds; it is not specifically directed to N-methyl benzomorphans, much less their levo or alpha-levo isomers. Of the compounds actually tested by May, only α-(±)-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan was found to have less physical dependence in monkeys than morphine; this compound is not an N-methyl benzomorphan—at the 2-position (see appealed claim 1) the substituent group is CH_2CH_2Ph, in contrast to appellants' CH_3. The only N-methyl benzomorphan for which May discusses addiction properties is α-(±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan. This compound was found to have a physical dependence in monkeys comparable to that of morphine. Thus, it is not seen how May would have suggested that the alpha-levo N-methyl benzomorphans would be nonaddictive.

As to Chignell et al., they state that α-(±)-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan (the racemate of the compound in appealed claims 5 and 10), like other members of the alpha series, "has little or no capacity to suppress withdrawal symptoms in monkeys," *i. e.*, little or no PDC. The May-Eddy affidavits establish that while this Chignell et al. racemate does, in fact, exhibit no PDC, it does *not* exhibit morphine antagonism. There is no evidence of record which would suggest that no PDC, *alone*, is evidence of nonaddictiveness. Thus, since the Chignell et al. racemate does not exhibit morphine antagonism, it would appear, from this record, that one skilled in the art would not expect

it to be nonaddictive. Considering the importance of nonaddictiveness in the field of analgesics (this statement will be developed hereinbelow), we find it difficult to believe that if Chignell et al. thought they had uncovered a nonaddictive analgesic, they would not have expressly so stated. Therefore, since Chignell et al.'s racemate does not in fact exhibit the property which, according to this record, those skilled in the art look for as evidence of nonaddictiveness, viz., morphine antagonism, we fail to see how it would have suggested the nonaddictiveness of appellants' compounds.

The Jacobson affidavit, particularly paragraphs 13 and 14, *supra*, is evidence that, according to the opinion of an expert in the field, *see In re Sebek*, 465 F.2d 904, 59 CCPA 1220, 175 USPQ 93 (1972), since analgesia and addiction liability cannot reliably be predicted on the basis of chemical structure, and since nonaddictive analgesia had not been previously established for any of the N-methyl benzomorphans, the combination of properties exhibited by appellants' compounds was unpredictable.

[6] Considering the entire record, including the fact that not a single reference relied upon by the PTO suggests that any N-methyl benzomorphan exhibits the combined properties of analgesic potency comparable to morphine coupled with nonaddictiveness, we are led to the inescapable conclusion that it was totally unexpected that appellants' levo and alpha-levo N-methyl benzomorphans would have exhibited such a combination of properties and, concomitantly, could be used to effect nonaddictive analgesia.

[7] Since the record reflects both an expected beneficial result, viz., potent analgesia, and an unexpected beneficial result, viz., nonaddictive, potent analgesia, it is necessary to determine the weight to be accorded each prior to making the ultimate determination on the issue of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (Cust. & Pat.App.1977); *cf. In re Murch*, 464 F.2d 1051, 59 CCPA 1277, 175 USPQ 89 (1972) (claimed thermoplastic blend had expected, improved blend toughness, but unexpected, improved weld line toughness); *In re Orfeo, supra* (expected that azeotrope could be used in claimed refrigeration process, but unexpected savings in power requirement).

The Jacobson affidavit indicates that "medicinal chemists have for many years been searching for an analgesic drug which has the analgesic potency of morphine, but without morphine's side effects and addiction liability." Moreover, Jacobson states that "[t]he discovery of a nonaddictive analgesic with analgesic potency comparable to that of morphine would eliminate a major medical problem and would be of inestimable value."

In further support of their position that nonaddictive analgesia was a highly significant result, appellants summarized for both the examiner and the board certain findings of fact of the District Court of the Southern District of Florida in the case of *Eli Lilly & Co. v. Generix Drug Sales, Inc.*, 324 F.Supp. 715, 169 USPQ 13 (D.C.Fla.1971), *aff'd.* 460 F.2d 1096, 174 USPQ 65 (CA5 1972).

Eli Lilly involved a suit for infringement of the patent covering alpha-dextro propoxyphene hydrochloride, marketed under the trademark "Darvon." This compound was the first synthetic analgesic of the morphine class, *i. e.*, centrally acting, having negligible hazard of addiction. The findings in *Eli Lilly* which we view as particularly illuminating are:

> 13. . . . [Darvon] satisfied a long-felt need for a synthetic analgesic having the pain-relieving properties of morphine but without addiction liability. That search began in the late 1920's . . . . [324 F.Supp. at 717.]
>
> 14. . . . To coordinate and foster . . . research [for a non-narcotic synthetic analgesic of the morphine class], the Committee on Drug Addiction and Narcotics (later renamed the Committee on Problems of Drug Dependence), a committee of experts formed and sponsored by the National Academy of Science, assumed responsibility for monitoring this work . . . .

By 1950, hundreds of compounds evidencing analgesic potency were being submitted for study in human beings for addiction liability . . . .

Lilly submitted . . . [Darvon]. The compound proved to be the first synthetic analgesic of the morphine class . . . having negligible hazard of addiction. Lilly introduced Darvon commercially in 1957, and since then Darvon has remained unique as the only such analgesic commercially available. [324 F.Supp. at 718.]

* * * * * *

23. . . . DARVON's medical and commercial acceptance was immediate and dramatic; . . . [it] has continued to stand as unique over years of continuing research for a drug of comparable characteristics . . . . [324 F.Supp. at 720–21.]

Neither the board nor the solicitor contests the substance of these findings or their status as admissible evidence in the record before the PTO.

[8] We agree with appellants that *Eli Lilly* is relevant. In *In re Cable*, 347 F.2d 872, 878, 52 CCPA 1561, 1569, 146 USPQ 175, 180 (1965), the court stated:

> Where affirmative evidence is of record bearing on the history of an art, it should be considered and given appropriate weight in arriving at an 'objective' vis-a-vis a 'subjective' determination of the issues arising under 35 U.S.C. § 103.

While the evidentiary value of *Eli Lilly* as establishing many unsuccessful attempts in the quest for a nonaddictive morphine substitute is diminished by the fact that those attempts occurred before May, the most pertinent reference, *In re Sabatino*, 387 F.2d 981, 986, 55 CCPA 811, 816, 156 USPQ 212, 216 (1968), we regard the above cited findings, as well as the Jacobson affidavit, as uncontroverted evidence that the *raison d' être* for research by those skilled in this art was, and still is, not simply to produce another analgesic compound, but to produce one which would exert this therapeutic value while at the same time being nonaddictive. This, in our view, diminishes the significance that should be attached to the expected beneficial result of potent analgesia, *i. e.*, it diminishes its evidentiary value that one skilled in the art would have been motivated to make appellants' compounds and to use them to effect analgesia, and enhances the significance that should be attached to appellants' unexpected result of nonaddictive, potent analgesia, *i. e.*, it enhances its evidentiary value as an objective indicium of nonobviousness.

[9] Balancing the prima facie case of obviousness made out by the PTO against appellants' objective evidence of nonobviousness, we hold that the subject matter of appealed claims 2–5 and 7–10 would not have been obvious to one of ordinary skill in the art.

Composition Claims

Preliminarily, we note that claims 11–13,[10] like method claims 2–5 and 7–10, recite a *novel* compound. *In re Williams, supra.* The board's treatment of the composition claims paralleled its disposition of claims 2–5 and 7–10. The board stated, in effect, that since the property of analgesic activity would have been expected, the fact that the prior art did not recognize another advantageous property, viz., nonaddictiveness, does not diminish the teaching of analgesic activity. We disagree.

In *In re Albrecht*, 514 F.2d 1389, 1395–96, 185 USPQ 585, 590 (Cust. & Pat.App.1975), the court stated:

> We are of the opinion that a novel chemical compound can be *nonobvious* to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound. [Emphasis in original.]

10. Since the only active ingredient in the composition claims is the compound, we will treat these claims as if they were compound claims.

Thus, *merely* because those skilled in the art would have expected the compound of claim 11 to have analgesic activity, does not mean, as the board apparently suggests, that an irrebuttable presumption of obviousness has been established. Those properties which would have been expected must be balanced against the unexpected properties. *In re Nolan, supra; cf. In re Murch, supra; In re Ruschig*, 343 F.2d 965, 52 CCPA 1238, 145 USPQ 274 (1965) (vague "basket" disclosure uses suggested by prior art, but no suggestion that claimed compound would be anti-diabetic agent). *See generally In re Papesch*, 315 F.2d 381, 50 CCPA 1084, 137 USPQ 43 (1963).

The solicitor cites *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (Cust. & Pat.App.1977) [hereinafter cited as *Wilder II*], as supportive of the board's decision. In *Wilder II*, appellant claimed a single compound which was disclosed as useful as an antidegradant in rubber and which unexpectedly had minimal toxicity to human skin. The prior art taught that the isomer and homologue of the claimed compound were useful as gasoline stabilizers. While appellant's affidavit evidence established reduced skin irritation using the claimed compound compared to the isomer, the evidence also illustrated that the homologue was a lesser irritant than the claimed compound. The prior art, however, was unaware of the homologue's low toxicity. Particularly relevant to the case at bar is the following discussion in *Wilder II, supra* at 460, 195 USPQ at 429:

> Wilder's discovery of the absence of skin toxicity in the claimed compound does not end the inquiry, because one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties. *In re Hoch*, supra [428 F.2d 1341, 57 CCPA 1292, 166 USPQ 406 (1970)]. Appellant has shown no *actual difference* [emphasis in original] in properties between the two compounds [claimed compound and prior art homologue] *or any other evidence sufficient to rebut that expectation.* [Emphasis added.]

Appellants, as in *Wilder II*, have shown an actual unexpected difference in properties between the claimed compound and its isomers [11] (only one isomer was involved in *Wilder II*). Also as in *Wilder II*, appellants' evidence establishes that a single prior art homologue (disclosed in May) of the claimed compound, to wit, α -(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, inherently possessed, unbeknownst to the prior art, the combination of properties of appellants' compound. The thin veneer of similarity between *Wilder II* and the case at bar ends there.

The appellant in *Wilder II* merely showed that while the isomer was toxic, the homologue and claimed compound were not. Although the court noted [*supra* at 461, 195 USPQ at 430] that this indicates "some degree of unpredictability," it concluded that, *on the record therein*, the claimed compound would have been obvious. As alluded to by the court, the basis of the prima facie case of obviousness, at least to a major extent, is based on the presumed expectation that compounds which are similar in structure will have similar properties. The *Wilder II* court recognized that a showing of actual difference in properties between the claimed compound and the structurally similar prior art compound over which it was rejected is *not* the only manner of rebutting this presumption. *See In re Hoch, supra. But see In re Wilder*, 429 F.2d 447, 57 CCPA 1314, 166 USPQ 545 (1970) (connected case to *Wilder II*). Implicit in *Wilder II* is that an applicant may rebut the aforementioned presumption by producing sufficient evidence which demonstrates a substantial degree of unpredictability in the pertinent art area.

11. The compound of claim 11 is α-(-)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan. As discussed *supra*, its isomers, *i. e.*, α-(+), α-(-), and β-(-)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, and its racemates, *i. e.*, α-(±) and β-(±), do not exhibit the *combined* test properties of an E.D.50 comparable to that of morphine sulphate, morphine antagonistic activity, no PDC, low toxicity, and a relatively high therapeutic index.

In contradistinction to the appellant in *Wilder II*, appellants here have established a substantial record of unpredictability vis-à-vis a highly significant combination of properties. The May-Eddy affidavits tested the α-(+), β-(−), β-(+) isomers, as well as the α-(±) and β-(±) racemates, of the claim 11 compound and the prior art compound, viz., α-(−)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan. Similar tests were conducted on the compounds in claims 3–5 and 8–10, which are homologues of the claim 11 compound, as well as on their isomers and racemates. Of the 21 compounds tested, only the levo[12] and alpha-levo compounds (five compounds) exhibited either morphine antagonistic activity or the combination of properties of no PDC coupled with morphine antagonistic activity. Moreover, appellants submitted the Jacobson affidavit which states, *inter alia*, that "analgesia and addiction liability cannot reliably be predicted on the basis of chemical structure." Thus, unlike the appellant in *Wilder II*, appellants here have satisfactorily rebutted the presumed expectation that structurally similar compounds have similar properties.

Balancing the prima facie case of obviousness made out by the PTO against appellants' objective evidence of nonobviousness, we hold that the subject matter of claims 11–13 would not have been obvious to one of ordinary skill in the art. *Compare In re Albrecht, supra; In re Murch, supra; In re Ruschig, supra; with In re Hoch, supra; In re Mod*, 408 F.2d 1055, 56 CCPA 1041, 161 USPQ 281 (1969); *In re de Montmollin*, 344 F.2d 976, 52 CCPA 1287, 145 USPQ 416 (1965).

Accordingly, for the reasons set forth herein, the decision of the board is *affirmed* as to claims 1 and 6 and *reversed* as to claims 2–5 and 7–13.

MODIFIED.

12. See note 7, *supra*.